## REMARKS

Applicants have carefully studied the Final Office Action mailed on June 4, 2002, which issued in connection with the above-identified application. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance or in better form for consideration on appeal. Entry of this amendment under 37 C.F.R. § 1.116, favorable reconsideration and allowance of the present claims are respectfully requested.

### Pending Claims

Claims 2-9, 11-25 and 27-57 were pending and at issue in the application. Claims 21-25 and 30-47 have been withdrawn from examination as being drawn to a non-elected invention. Claims 2-9, 11-20, 27-29, and 48-57 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 2-9, 13-20, 27-29, and 48-57 have been rejected under 35 U.S.C. §102(e) and/or under 35 U.S.C. §103(a) as being anticipated by or obvious over the prior art.

Claims 21-25 and 30-47 have been canceled as drawn to a non-elected invention. Claims 4-9, 17-20 and 52-53 have been canceled. Claims 3, 14, 16, 28, 50, 54, 56, and 57 have been amended to correct formal defects. Claims 2, 13, 15, and 49 have been rewritten in independent form and amended to correct formal defects. Claims 27, 29, 48, 51, and 55 have been amended and new claims 58-62 have been added in order to more particularly point out and distinctly claim the invention. Claims 27, 29 and 55 as amended are directed to the subject matter of the original claims 26 and 28. Claim 48 as amended is directed to the subject matter of the original claims 1, 2 and 4. Claim 51 as amended is directed to the subject matter of the original claims 10, 13 and 15. Accordingly, these claims find support in the respective original

claims. Specific support for new claims 58-62 can be found, for example, at p. 7, l. 29 - p. 8, l. 10, p. 12, ll. 13-19, p. 29, l. 26 - p. 30, l. 3, and Example 3 (in particular, p. 52, l. 8 - p. 53, l. 5 and p. 53, l. 28 - p. 54, l. 24) of the present specification. Specific support for the recitation "the 5' untranslated region of *CASP8* genomic DNA" in claims 29 and 60 can be found, for example, at p. 8, ll. 7-10 and p. 12, ll. 13-16. No new subject matter has been added as a result of these amendments; no new search is required, and no new issues are raised. Upon entry of these amendments, claims 2-3, 11-16, 27-29, 48-51, and 54-62 will be pending.

**35 U.S.C. §112, Second Paragraph, Rejections**

In the Action, claims 2-9, 11-20, 27-29, and 48-57 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner contends that the term "poor prognosis" in claims 11-20 and 51-54 is a relative term. As claims 17-20 and 52-53 have been canceled and the remaining claims have been amended to delete the term "poor prognosis", the rejection is rendered moot. The Examiner further states that the newly added recitation "proper cellular regulation" in claims 2-9, 11-20, 27-29 and 48-57 is indefinite. Applicants respectfully note that the rejection of claims 56 and 57 is improper, because these claims do not recite the term "proper cellular regulation". As claims 4-9, 17-20 and 52-53 have been canceled and the remaining claims have been amended to delete the term "proper cellular regulation", the rejection is rendered moot.

In light of the foregoing, applicants respectfully submit that the rejection of the claims based upon 35 U.S.C. §112, second paragraph, is overcome and withdrawal of such is kindly requested.

**35 U.S.C. §102(e) Rejection**

In the Office Action, the Examiner has maintained the rejection of claims 2-3, 6-9, 13-14, 17-20, 27-29 and rejected the newly added claims 48-53 and 55 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,172,190 to Hunter *et al.* (hereinafter "the '190 patent"). The Examiner maintains that the '190 patent anticipates these claims because it teaches a method of diagnosis or prognosis of a disorder associated with apoptotic cell death by detecting inactivation of the *CASP8* gene by detecting modification of the *CASP8* genomic DNA. The Examiner also states that the '190 patent teaches detecting the *CASP8* gene inactivation using such methods as (i) immunoassay to detect the lack of CASP8 protein and (ii) labeled nucleotide probes or PCR primers to detect the modification of *CASP8* DNA.

As claims 6-9, 17-20 and 52-53 have been canceled, the rejection of these claims is rendered moot.

With respect to the remaining claims, the rejection is respectfully traversed. These claims call for detecting inactivation of a *CASP8* gene expression (*e.g.*, in a method for diagnosis or prognosis of a cancer) by detecting (i) methylation of *CASP8* genomic DNA, (ii) the absence of expression of CASP8 protein, or (iii) the absence of a *CASP8* mRNA. Applicants respectfully submit that the '190 patent fails to teach detecting inactivation of a *CASP8* gene expression by any of these methods and fails to teach how *CASP8* is inactivated in cancer.

As specified in the applicants' response to the previous Office Action, the '190 patent is directed to two truncated forms of CASP8 protein, Caspase-8h and Caspase-8i. In contrast to the present application, which discloses and claims that cancers associate with a mutated *CASP8* allele that produces no protein and is neither able to partially fulfill the function of the wild-type protein nor to inhibit it, Caspase-8h and Caspase-8i proteins disclosed in the '190 patent are expressed, exert biochemical function, and affect CASP8-mediated apoptosis signaling cascade. In contrast to the present claims, the genomic DNA encoding the Caspase-8h

and Caspase-8i proteins is the same DNA that encodes the full-length CASP8, *i.e.*, it does not contain any modifications or deletions of the *CASP8* genomic DNA. The truncation of Caspase-8h and Caspase-8i proteins is a result of the alternative splicing, which is a regulated posttranscriptional process.

Most importantly, in contrast to the methods recited in the present claims, the '190 patent does not teach the detection of the lack of the full-length CASP8 mRNA or protein, rather it teaches quantitating Caspase-8h or Caspase-8i mRNA or quantitating Caspase-8h or Caspase 8i protein[1]. Furthermore, contrary to the Examiner's assertion, although the '190 patent describes that oligonucleotide probes and PCR primers can be used for the identification of gene mutations[2], it does not disclose or suggest any methods for detecting methylation of *CASP8* genomic DNA or the absence of *CASP8* mRNA.

As noted above, the '190 patent fails to teach how *CASP8* is inactivated in cancer. In fact, col. 11, ll. 31-37 of the '190 patent state that "the novel forms of Caspase-8 described herein (Caspase-8h and Caspase-8i) ... would effectively compete with full length Caspase-8 for binding to FADD/MORT1 and thereby prevent the cell from undergoing apoptosis." This suggests that the presence of the Caspase-8h and Caspase-8i proteins interferes with the CASP8 full-length protein function; therefore contributing to the disruption of apoptosis and ultimately cancer.

Accordingly, applicants respectfully submit that the rejected claims are not anticipated by the '190 patent. Reconsideration and withdrawal of the anticipation rejection is believed to be in order.

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[1] Applicants respectfully note that the Examiner's statement at page 6 of the Office Action that col. 7, ll. 50-67 and col. 21, l. 16 - col. 22, l. 7 of the '190 patent teach or suggest the detection of the absence of expression of CASP8 is incorrect. All these sections teach is quantitating Caspase-8h and Caspase-8i mRNA or protein.

[2] *See, e.g.*, column 5, lines 27-30.

**35 U.S.C. §103(a) Rejections**

In the Action, claims 2-3, 6-9, 13-14, 17-20, 27-29, 48-53, and 55 have been also rejected under 35 U.S.C. §103(a) as being obvious over Mandruzzato *et al.* (J. Exp. Med., 186: 785-793, 1997) in view of the '190 patent or PCT Application No. WO 97/46662 by Dixit *et al.* (hereinafter "WO 97/46662"). The Examiner maintains that Mandruzzato teaches a method of diagnosis or prognosis of a cancer by detecting inactivation of a *CASP8* gene, said method comprising detecting a modification of *CASP8* genomic DNA. The Examiner relies secondarily upon the '190 patent or WO 97/46662 to show detection methods for gene inactivation such as (i) immunoassay to detect a lack of protein and (ii) labeled oligonucleotide probes or PCR primers to detect the modification of DNA. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use the methods of determination of gene inactivation taught by the '190 patent or WO 97/46662, to detect *CASP8* gene modifications taught by Mandruzzato.

In the Action, the Examiner has also rejected claims 2-9, 13-20, 27-29, and 48-57 as obvious in view of the references noted above and further in view of the two Herman *et al.* references noted in the previous Office Action (Proc. Natl. Acad. Sci. USA, 93: 9821-9826, 1996 and *ibid.* 91: 9700-9704, 1994). With respect to Herman references, the Examiner maintains that it would be obvious to use the detection of gene methylation (*e.g.*, using methylation PCR) taught by Herman to detect modifications of the *CASP8* gene taught in Mandruzzato. The Examiner concludes that Mandruzzato discloses that other mutations of *CASP8* are helpful in tumor studies and in this way provides a motivation for one of ordinary skill in the art to use the methods for determination of gene inactivation taught in the '190 patent and WO 97/46662, or to detect *CASP8* promoter methylation using the methods of Herman.

As claims 6-9, 17-20 and 52-53 have been canceled, the rejection of these claims is rendered moot.

With respect to the remaining claims, applicants respectfully traverse the rejection and submit that, even if taken together, the cited references do not disclose or suggest the methods and kits recited in the present claims and necessarily fail to provide a reasonable expectation of achieving the invention.

The courts have held that where the prior art seeks to solve the same problem as the claimed invention but lacks significant elements of the claimed invention, it is improper to view the invention in a piecewise fashion to find its elements in the prior art. On the contrary, the invention must be viewed as a whole. *Gore*, 721 F.2d 1540 (Fed. Cir. 1983); and *Phillips*, 673 F. Supp. 1278 (D. Del. 1987). Even where the elements of the claimed invention are known, the claimed invention may still be patentable. *Gillette*, 919 F.2d at 725. Further, it is improper to use hindsight to combine elements found in the prior art to reconstruct the claimed invention. *Gore*, 721 F.2d at 1552. In considering obviousness, the critical inquiry is whether something in the prior art as a whole suggests the desirability, and thus the obviousness, of making a combination. *In re Newell*, 891, F.2d 899, 901-02, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir.1992). The Examiner must show some objective teaching from the art that would lead an individual to combine the references, *i.e.*, there must be motivation. In particular, the mere fact that the teaching of a reference may be modified in some way so as to achieve the claimed invention does not render the claimed invention obvious unless the prior art suggested the desirability of the modification (emphasis added). *In re Fritch*, 972 F.2d 1260, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir.1992) and see also *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063 (Bd. Pat. App. & Intf. 1993). In other words, determination that the invention is obvious requires that (i) cited references teach the claimed invention as a whole, and (ii) both the suggestion of making the invention, and a reasonable expectation of success can be found in the prior art, not in the applicants' disclosure. MPEP Section 2143; *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully submit that the

Examiner's rejection again does not meet these criteria. None of the references cited in the instant Office Action provides a suggestion to be combined with the other references or to modify the disclosed methods, so that they in any way suggest the methods recited in the present claims.

The present claims call for detecting inactivation of a *CASP8* gene expression (*e.g.*, in a method for diagnosis or prognosis of a cancer) by detecting (i) methylation of *CASP8* genomic DNA, (ii) the absence of expression of CASP8 protein, or (iii) the absence of a *CASP8* mRNA. According to the present invention, cancers associate with a *CASP8* allele modified so that it produces no protein and therefore is neither able to partially fulfill the function of the wild-type protein nor to inhibit it.

As affirmed by the Examiner at pages 7 and 9 of the Office Action, in contrast to the instant claims, Mandruzzato fails to teach detection of *CASP8* gene modification, including a lack of expression of a *CASP8* allele, using nucleic acid primers, detection by immunoassay, or detection of the methylation of *CASP8* promoter.

In contrast to the present invention, in the carcinoma cell line described in Mandruzzato, both *CASP8* alleles are expressed. One allele expresses a wild-type CASP8 protein, and the other allele expresses a mutated CASP8 protein with 88 extra residues at the C-terminus, which is partially functional in apoptosis. In other words, the only *CASP8* mutation described by Mandruzzato *et al.* is a single nucleotide change (*i.e.*, a point mutation) within the *CASP8* coding sequence, which eliminates the stop codon, increasing the size of the encoded CASP8 protein by 88 amino acids. As further discussed in the article (e.g., at p. 790, right col., par. 4), this mutation may have a partially dominant effect. Although Mandruzzato suggests that mutations in other parts of the *CASP8* coding sequence resulting in the production of mutant proteins may be observed in other tumors[3], it does not disclose or suggest that the absence of

[3] *See* p. 791, top of right col.

CASP8 protein expression from at least one of the alleles may also associate with cancer. This difference between Mandruzzato and the present application, is particularly evident from the absence of any disclosure or suggestion in Mandruzzato of the modifications in the non-coding regions of the *CASP8* gene, such as the 5' untranslated region.

Accordingly, in contrast to the present invention, Mandruzzato does not teach that inactivation of *CASP8* gene in cancer results from the absence of expression of one or both *CASP8* alleles nor does it teach any alteration outside the coding region of *CASP8* (*e.g.*, methylation of the 5' untranslated region of the *CASP8* genomic DNA).

The '190 patent discloses two truncated forms of CASP8 protein, Caspase-8h and Caspase-8i, which are able to compete with the wild-type CASP8 for the interactions with other molecules in the apoptosis signaling cascade. As specified above, in contrast to the present invention, which discloses modifications or deletions of *CASP8* genomic DNA resulting in inactivation of *CASP8* gene expression, the '190 patent teaches that the genomic DNA encoding the Caspase-8h and Caspase-8i proteins does not contain any modifications or deletions compared to the genomic DNA encoding the full-length CASP8 protein. Furthermore, as noted above, the '190 patent fails to teach how *CASP8* is inactivated in cancer.

Most importantly, although the '190 patent describes that oligonucleotide probes and PCR primers can be used for the identification of gene mutations, it does not disclose or suggest that these reagents can be used to detect *CASP8*-inactivating modifications resulting in the absence of expression of at least one *CASP8* allele. Thus, as specified above, the '190 patent does not disclose or suggest any methods for detecting methylation of *CASP8* genomic DNA or detecting the lack of the full-length CASP8 mRNA or protein. Instead, it only teaches quantitating Caspase-8h or Caspase-8i mRNA or quantitating Caspase-8h or Caspase 8i protein.

Moreover, the '190 patent teaches away[4] from using an immunoassay to detect the absence of expression of the full-length CASP8 protein. Thus, as stated in col. 18, ll. 25-30 of this patent, "[p]referably, the antibodies recognize epitopes of Caspase-8h or Caspase-8i that are unique, i.e., are not present on other forms of Caspase-8 or more distantly related proteins. Accordingly, the antibodies are preferably raised against a peptide sequence present in Caspase-8h or Caspase-8i that is not present in other forms of Caspase-8..."

Similarly to the '190 patent, WO 97/46662 also does not disclose or suggest that oligonucleotide probes and PCR primers can be used to detect gene-inactivating modifications resulting in the absence of expression of at least one *CASP8* allele. Although WO 97/46662 teaches the polypeptides and DNA of *CASP8*[5] and detection of a mutated form of ICE LAP-7 (CASP8), in contrast to the present invention, it does not teach a lack of the expression of the gene by methylation or deletion of the gene.

Herman references do not cure any of the deficiencies of other cited references. Although they teach methylation (including methylation of a promoter region) as a mechanism for silencing of tumor-suppressor genes, they do not teach or suggest methylation of *CASP8* genomic DNA or any other gene modification leading to the lack of expression of CASP8 protein. Applicants respectfully note that there is no evidence in any of the other cited references that *CASP8* is methylated nor that such a methylation would cause inactivation of the *CASP8* gene. Therefore, one skilled in the art would not be motivated to look for methylation or lack of expression of CASP8 protein based on the combination of these references, *i.e.*, there is no motivation to combine Herman with the other references.

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[4] Where prior art references teach away from the claimed invention, it has been held that the claimed invention is nonobvious. *W.L. Gore & Associates., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1551-2 (Fed. Cir. 1983).

[5] Applicants note that the statement found on page 9, 1st paragraph of the response to the previous Office Action "WO 97/46662 teaches ICE LAP-7, which interacts with FLICE, which is another name for CASP-8" is incorrect.

Applicants respectfully submit that the Examiner's position that Mandruzzato discloses that other mutations of *CASP8* are helpful in tumor studies and in this way provides a motivation for one of ordinary skill in the art to detect *CASP8* promoter methylation using the methods of Herman, is incorrect. Methylation is not a DNA mutation; therefore, Mandruzzato does not provide any guidance or motivation to detect *CASP8* methylation in the 5' untranslated region. On the contrary, by emphasizing the importance of mutations in the coding region, Mandruzzato teaches away from detecting DNA modifications (such as methylation) in the non-coding regions of the *CASP8* gene.

It follows that, based on the disclosure of Mandruzzato (even if taken together with the '190 patent, and WO 97/46662) a person of ordinary skill in the art would not be motivated to apply the method of Herman (*i.e.*, methylation-sensitive PCR) to detect a DNA modification leading to the inactivation of *CASP8* gene expression.

In summary, the combined cited references do not provide a reasonable expectation of success much less a suggestion of the methods and kits recited in the present claims. The actual teachings of the references taken as a whole do not suggest the claimed invention, and the rejection requires impermissible hindsight reconstruction of various unconnected bits and pieces of the references to sustain itself. It is well settled however, that such hindsight reconstruction is an error. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *Fritch*, 23 U.S.P.Q.2d at 1784. The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]". *Dow Chemical Co.*, 5 U.S.P.Q.2d at 1532.

Accordingly, applicants respectfully submit that, even if taken together, the cited references do not disclose or suggest the methods and kits encompassed by the present claims. It follows that the new claims and rejected claims are not obvious over the cited art. Reconsideration and withdrawal of the obviousness rejection is believed to be in order.

## CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 2-3, 11-16, 27-29, 48-51, and 54-62 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

Dated: December 4, 2002

Irina E. Vainberg, Ph.D.
Reg. No. 48,008
Agent for Applicant(s)

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700
IEV:

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Vincent J. KIDD et al.

Serial No.: 09/477,082 Group Art Unit: 1642

Confirmation No.: 8684

Filed: December 30, 1999 Examiner: Jennifer Hunt

For: TUMOR SUPPRESSOR PROTEIN INVOLVED IN DEATH SIGNALING, AND DIAGNOSTICS, THERAPEUTICS, AND SCREENING BASED ON THIS PROTEIN

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**MARK-UP FOR AMENDMENT OF DECEMBER 4, 2002**

Pursuant to 37 C.F.R. §1.121, applicants provide the following mark-up copy of the amendments requested for the claims in the above-referenced application. This document is submitted simultaneously with an Amendment and Response to the Final Office Action mailed on June 4, 2002.

**CLAIMS:**

2. (Amended) A [The] method for detecting [according to claim 48, wherein the modification of genomic DNA resulting in] inactivation of a *CASP8* gene expression, [is detected by] comprising detecting the absence of expression of a CASP8 protein [in a sample from a cell].

3. (Amended) The method according to claim 2, wherein the absence of expression of a CASP8 protein is detected by a method selected from the group consisting of immunoassay and biochemical assay.

4-9. Canceled

11. (Unchanged) The method according to claim 51, wherein the cancer is a tumor in which a *myc* gene is amplified.

12. (Unchanged) The method according to claim 51, wherein the cancer is a neuroblastoma.

13. (Amended) A [The] method [according to claim 51, wherein the modification of genomic DNA resulting in] for diagnosis or prognosis of a cancer comprising detecting inactivation of a *CASP8* gene expression, wherein said method comprises [is detected by] detecting the absence of expression of a CASP8 protein [in a sample from a cell].

14. (Amended) The method according to claim 13, wherein the absence of expression of a CASP8 protein is detected by a method selected from the group consisting of immunoassay and biochemical assay.

15. (Amended) A [The] method [according to claim 51] for diagnosis or prognosis of a cancer comprising detecting[, wherein the modification of genomic DNA resulting in] inactivation of a *CASP8* gene expression, wherein said method comprises detecting [is] a methylation of *CASP8* [promoter] genomic DNA.

16. (Amended) The method according to claim 15, wherein the methylation of [the] *CASP8* [promoter] genomic DNA is detected by methylation polymerase chain reaction (PCR) assay.

17-20. Canceled

27. (Amended) The kit of claim 55, wherein the detection assay is [an immunoassay] a polymerase chain reaction (PCR) assay.

28. (Amended) The kit of claim [55] 27, wherein the detection assay comprises oligonucleotide PCR primers for amplification of at least a part of *CASP8* genomic DNA.

29. (Amended) The kit of claim [55] 27, wherein the detection assay comprises [a labeled] oligonucleotide [of at least 15 bases that specifically hybridizes to] PCR primers for amplification of at least a part of the 5' untranslated region of *CASP8* genomic DNA.

48. (Amended) A method for detecting inactivation of a *CASP8* gene expression, comprising at least one assay selected from the group consisting of detecting a [modification] methylation of *CASP8* genomic DNA [comprising the *CASP8* gene, wherein such a modification results in], detecting the absence [of expression of at least one *CASP8* allele and reduction in the total level] of expression of a CASP8 protein [to below that necessary for proper cellular regulation], and detecting the absence of a *CASP8* mRNA.

49. (Amended) A [The] method for detecting inactivation of a *CASP8* gene expression, comprising [according to claim 48, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is detected by] detecting the absence of a *CASP8* mRNA [in a sample from a cell].

50. (Amended) The method according to claim 49, wherein the absence of a *CASP8* mRNA is detected by a method selected from the group consisting of Northern blotting and reverse transcriptase-polymerase chain reaction (RT-PCR) assay.

51. (Amended) A method for diagnosis or prognosis of a cancer comprising detecting inactivation of a *CASP8* gene[, wherein inactivation of the *CASP8* gene results in the absence of] expression, wherein said method comprises [of] at least one assay selected from the group consisting of detecting a methylation of *CASP8* genomic DNA, detecting the absence [*CASP8* allele and reduction in the total level] of expression of a CASP8 protein [to below that necessary for proper cellular regulation, and is indicative of the presence of a cancer or a poor prognosis for outcome of treatment of the cancer by conventional therapies], and detecting the absence of a *CASP8* mRNA.

52-53. Canceled

54. (Amended) The method according to claim [51] 48, wherein the [modification of genomic DNA resulting in] inactivation of a *CASP8* gene expression is selected from the group consisting of homozygous deletion, heterozygous deletion coupled with gene silencing by methylation, and homozygous gene silencing by methylation.

55. (Amended) A kit for detecting inactivation of a *CASP8* gene expression, comprising an assay for detecting [a modification of genomic DNA comprising the *CASP8* gene, wherein such a modification results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation] a methylation of *CASP8* genomic DNA.

56. (Amended) A method for detecting inactivation of a *CASP8* gene expression, comprising detecting a methylation of *CASP8* genomic DNA [comprising the *CASP8* gene promoter].

57. (Amended) The method according to claim 56, wherein the methylation of [the] *CASP8* [promoter] genomic DNA is detected by methylation polymerase chain reaction (PCR) assay.

58. (New) The kit of claim 29, wherein the detection assay comprises oligonucleotide PCR primers for amplification of SEQ ID NO: 1 or SEQ ID NO: 2.

59. (New) The kit of claim 58, wherein the detection assay comprises at least one oligonucleotide PCR primer selected from the group consisting of SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

60. (New) The method according to claim 56, wherein the methylation occurs in the 5' untranslated region of *CASP8* genomic DNA.

61. (New) The method according to claim 60, wherein the methylation occurs in sequences selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2.

62. (New) The method according to claim 57, wherein the PCR assay utilizes at least one of the primer sequences selected from the group consisting of SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

Respectfully submitted,

Dated: December 4, 2002

Irina E. Vainberg, Ph.D.
Reg. No. 48,008
Agent for Applicant(s)

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

IEV: